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Effect of chronic calcium-channel blockers therapy on clinical and angiographic outcomes of radial artery grafts: an analysis of the RADIAL database

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Abstract

Aim: To evaluate if chronic calcium-channel blocker therapy (CCB) influences the mid-term clinical and angiographic outcomes of radial artery (RA) grafts used for coronary bypass surgery (CABG).

Methods: The patient-level data of all six angiographic randomized trials that evaluated RA graft status at mid-term follow-up were joined in a common database. Cox regression analysis was used to evaluate the effect of CCB on the incidence of a composite of major adverse cardiac events (death, myocardial infarction and repeat revascularization MACE) and graft occlusion. Variables tested were: CCB, age, gender, diabetes, previous myocardial infarction, surgical priority, renal insufficiency, target vessel, percentage of target vessel stenosis ≥90%, and location of proximal anastomosis.

Results: The final study population included 732 patients (502 treated with CCB). The cumulative incidence of MACE 3, 6 and 9 years was 3.7% vs. 9.3%, 13.4% vs 17.6% and 16.8% vs 20.5% in the CCB and no CCB groups respectively (log-rank P=0.003). After controlling for confounders, CCB therapy was independently associated with a significantly lower risk of MACE (hazard ratio (HR) 0.53; 95%confidence interval (CI) 0.31-0.89; P=0.01). The cumulative incidence of RA occlusion at 3, 6 and 9 years was 0.9% vs. 8.6%, 9.6% vs 21.4% and 14.3% vs 38.9% in the CCB and non-CCB group respectively (log-rank P<0.001). After controlling for confounders, CCB therapy was significantly associated with reduce graft occlusion (HR 0.20; 95%CI 0.08-0.50; P<0.001). One year of CCB was associated with a reduction in MACE compared to shorter term treatment (P<0.001).

Conclusion: CCB is associated with significantly better mid-term clinical and angiographic RA outcomes. Our results support the routine use of CCB after CABG using the RA.

Introduction

The RADIAL (Radial Artery Database International ALliance) project is a combined patient-level dataset including all the randomized trials (RCT) and many observational studies that have compared the radial artery (RA) with other conduits at mid-term follow-up. In a recent publication from the RADIAL database we have shown for the first time using randomized data that the use of the RA as the second conduit for coronary artery bypass (CABG) is associated with a significant reduction in the risk of mid-term cardiac events compared to the use of the saphenous vein (1).

Although in recent years the use of the RA has been very limited among the surgical community, the publication of the results of the primary analysis of RADIAL and the consequent Class I indication in the 2018 ESC/EACTS Guidelines, is likely to elicit renewed interest for the artery and the issues related to its use for CABG. One of the most important unsolved questions is the role of chronic calcium-channel blocker therapy (CCB) for CABG patients who received one or more RA grafts.

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In fact, due to the thick muscular wall of the RA and of the concerns of graft spasm, CCB is traditionally prescribed postoperatively for CABG RA patients (2). This practice, however, is weakly supported by the published literature.

Only few studies to date have evaluated the effect of CCB on the angiographic and clinical outcome of RA grafts and, in most cases, the results have been neutral (3). One major problem is that, due to the high patency rate and excellent clinical outcome of the RA, a very large sample size is required to detect even moderate differences in angiographic and clinical outcomes. All the published series were very likely largely underpowered for this purpose.

CCB is associated with non-negligible side-effects and costs (4). Also, due to its hypotensive effect, the use of CCB may preclude the use of other evidence-based therapy such as beta blockers or angiotensin converting enzyme inhibitors. For these reasons the evaluation of CCB efficacy in patients with RA grafts is of major relevance for the patients and the community.

Our primary study objective was to assess whether CCB use after RA CABG affects the midterm clinical and angiographic outcomes, and address the power limitations by pooling individual patient data.

Methods

Dataset

The RADIAL (Radial Artery Database International ALliance) initiative was created in March 2015 with the aim to combine dataset from trials on the RA to facilitate meta-analytic studies. Details of the projects have previously been published (1). The list of the RADIAL investigators is enclosed in **Supplementary Table 1**.

The present analysis includes individual patient level data from all patients who received the RA in the published RCTs comparing the long-term (≥2 years) outcomes of the RA and other conduits. The 6 RCTs included are: the Radial Artery Patency and Clinical Outcomes (RAPCO, groups 1 and 2), the Radial Artery Patency Study (RAPS), Radial Artery Versus Saphenous Vein Patency Study (RSVP), Petrovic, Stand-in-Y and Yoo trials (5-10).

Postoperative CCB was recommended per protocol in each of the individual trials, with differences in the type of drug used and the duration of the treatment (**Table 1**).

The RA was used on the second most important coronary target vessel in all trials except for RAPS. In RAPS, within-patient randomization was used and patients with three vessel disease were randomized to receive both a saphenous vein and a RA graft randomly allocated to the right or the circumflex coronary artery. For this reason in RAPS the RA was used on either the second or third most important target coronary vessel. To minimize confounders, data from RAPS were not used for the main analysis. A sensitivity analysis of RA graft occlusion including the individual patient data from RAPS was performed (see Appendix).

Outcomes

The primary outcome was a composite of major adverse cardiac events (death, myocardial infarction and repeat revascularization - MACE) at maximum follow-up. The secondary outcome was RA graft occlusion at maximum follow-up. Patency rate was graded according to Fitzgibbon classification (11). Grade A and B were considered patent and grade O occluded. Individual components of the primary composite outcome were also analyzed individually.

Statistical analysis

Continuous variables were tested for normality and were reported as means and standard deviations and compared with a 2-way analysis of variance stratified by trial. Baseline categorical variables were reported as counts and percentages and compared with a conditional regression analysis stratified by trial. Outcomes were reported as a cumulative incidence and the CCB and non-CCB groups were compared using log-rank test stratified for individual trials. For the primary composite endpoint of death, myocardial infarction and repeat revascularization and for RA graft occlusion, cumulative incidences were graphically presented using Kaplan Meier estimates (survival and survminer R package). Treatment effect estimates on primary endpoints was calculated using multivariable Cox models stratified for individual trials and reported as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazard assumptions were verified using the Schoenfeld residuals.

As a sensitivity analysis, the effect of CCB therapy on MACE was tested forcing CCB as a time dependent covariate according to the duration based on individual study protocol. Moreover, the effect of CCB therapy was adjusted for other medications included in the individual study protocols including statins and beta blockers (all patients received aspirin). Finally, we investigated whether CCB therapy duration influenced the incidence of primary outcomes (MACE and graft occlusion) by forcing CCB therapy duration (as linear or spline terms) in a Cox regression model (patients who did not receive CCB therapy included as CCB duration =0). Non-linearity between CCB therapy duration and incidence of MACE was tested by means of ANOVA test and the model with highest X^2 and lowest degree of freedom was selected (restricted cubic spline 2 knots). Covariates included in the Cox models were: CCB, age, gender, diabetes, previous myocardial infarction, surgical priority, renal insufficiency, target vessel, percentage of target vessel stenosis ≥90%, and location of RA proximal anastomosis, statin therapy and beta-blocker therapy.

Results

The study population included 732 patients (502 treated with CCB). Details of the baseline and intraoperative characteristics of patients of the two group are given in **Table 2**.

Mean clinical follow-up was 60±27 months. The main clinical outcomes are summarized in **Table 3**. The cumulative incidence of MACE at 3, 6 and 9 years was 3.7% vs. 9.3%, 13.4% vs 17.6% and 16.8% vs 20.5% in the CCB and no CCB groups respectively (log-rank P=0.003). After controlling for confounders, CCB therapy was independently associated with a significantly lower risk of MACE (HR 0.53; 95%CI 0.31-0.89; P=0.01, see **Table 4** and **Figure 1**). The incidence of the individual components of the composite outcome was reduced, significantly so for MI.e.

Protocol-driven angiographic follow-up was available in 243 patients in the CCB group and 200 in the non-CCB. Mean time to angiographic follow-up was 55±20 months. The cumulative incidence of RA occlusion at 3, 6 and 9 years was 0.9% vs. 8.6%, 9.6% vs 21.4% and 14.3% vs 38.9% in the CCB and non-CCB group respectively (log-rank P<0.001). After controlling for confounders, CCB therapy was significantly associated with a lower risk of graft occlusion (HR 0.20; 95%CI 0.08-0.50; P<0.001 **Table 5** and **Figure 2**). Clinical and angiographic outcomes stratified by trial are reported in **Supplementary Table 2**.

CCB therapy was confirmed to be associated with a lower risk of MACE when CCB therapy was forced as a time dependent covariate (HR 0.35; 95%CI 0.12-0.99; P=0.045) and also when adjusted for other medications used in the individual study protocols for secondary prevention (HR 0.41; 95%CI 0.22-0.74; P=0.003). When the duration of CCB therapy was tested we found a non-linear negative association between the duration of CCB therapy and the risk of MACE (P<0.001, Figure 3) and graft failure (P= 0.03; Figure 4). Specifically, we found that 1 year of CCB therapy was associated with a greater reduction in MACE than a shorter duration of CCB treatment (P<0.001). A benefit of a longer duration of CCB therapy was not be demonstrated (P=0.08), although the numbers of patients on prolonged CCB therapy was small. A similar relationship was found between CCB therapy duration and the risk of graft occlusion, with a significant reduction of graft occlusion for CCB therapy lasting 1 year comparing to shorter period (P=0.006) but a further trend could not be demonstrated with longer treatment (P=1).

The sensitivity angiographic analysis including RAPS confirmed the robustness of the primary analysis (**Supplementary Table 3 and 4**).

Discussion

In this patient-level pooled analysis of all the RCTs on the mid-term clinical and angiographic outcomes of RA graft we found that the use of CCB was associated with a significantly lower risk of MACE and higher RA patency rate.

Among all the conduits used for CABG, the RA is the only muscular artery. Histologic studies have shown that the thickness of the muscular component of the RA is almost twice that of the internal thoracic artery (12). This thick muscular media is the anatomic explanation of the well-known hyper-reactivity of RA rings reported in pharmacological studies. Chardigny and coauthors in a classic organ bath studies have shown that the spastic response of the RA to norepinephrine, serotonin, and thromboxane A2 is significantly higher than that of any other conduit used for CABG (13).

Those peculiar morpho-functional features of the RA and the consequent concerns of postoperative RA spasm are the reasons behind the empiric use of CCB in patients with RA grafts.

It must be noted, that in the years after implantation in the coronary circulation, RA grafts lose most of the muscular component of the media and of their spastic tendency, becoming very similar to internal thoracic artery grafts (14). On this basis, it is possible that the benefits of CCB are limited to the early postoperative period. In fact, most of the trials included in the analysis used CCB only for the first 6-12 months after surgery.

The previous literature on the effect of CCB in patients with RA graft is controversial.

Two small previous randomized trials reported that the use of CCB during the first postoperative year and in the following years did not affect graft patency, graft reactivity, scintigraphically-evident myocardial ischemia or clinical outcomes (15, 16). In a small angiographic series, Moran and colleagues found similar clinical outcomes and angiographic patency among RA patients who received CCB or not (17). Similarly, a post-hoc analysis of the Radial Artery Patency Study found that the incidence of string sign (the highest degree of RA graft spasm) was not affected by the compliance with the prescribed postoperative CCB, although compliance with CCB use was high(18).

Due to the very high patency rate and excellent clinical outcomes of RA grafts however it is very likely that the individual published studies were largely underpowered to detect even moderate differences in outcome.

Despite this lack of solid evidence, CCB is routinely prescribed in most centers after RA grafting.

A 2003 survey of all Canadian cardiac surgery centers reported that some form of anti-spastic therapy was adopted in almost all institutions (25/27) after RA grafting (2) and to our knowledge, similar postoperative protocols are used in other parts of the world.

The chronic use of calcium channel blockers or other anti-spastic agent is associated with non-negligible side-effects and considerable costs. In a large community-based study, Kloner and associates reported that edema occurred in 24% of the patients on chronic therapy with amlodipine, headache in 8.8% and fatigue and dizziness in more than 4% (19). For these reasons, an objective evaluation of the effect of CCB in patients with RA grafts is of relevance for the patients and cardiovascular community.

Our data suggest that in patients with RA grafts, the use of CCB for at least the first 12 months is associated with better clinical and angiographic outcomes.

Some limitations of this analysis must be acknowledged. The different trials used different protocols and pharmacological agents for CCB. Differences were also present in the surgical technique and in the follow-up time. Although the original studies were randomized and had similar inclusion criteria, this post-hoc analysis shares the limitations of observational studies.

However, only limited heterogeneity between trials was noted and we adjusted our results for clinical and angiographic confounders using regression. Of note, this is the first study of sufficient sample size to investigate the effect of CCB on the clinical and angiographic outcome of RA grafts.

In conclusion, our results show that the use of CCB is associated with higher patency rate and better clinical outcomes at 5 years in patients with RA grafts. Those data support the routine use of CCB, at least for the first 12 months after CABG using the RA.

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Table 1. **Details of the calcium channel blockers therapy and other secondary prevention therapies in the individual trials.**

Trial	Details of postoperative therapy
Petrovic	any CCB for 1 year + statins + beta blockers + aspirin
RAPCO	amlodipine for 6 months+ aspirin
RAPS	nifedipine for 6 months (diltiazem or amlodipine if intolerant) + statins + aspirin
RSVP	diltiazem for 6 weeks + aspirin
Stand-in-Y	diltiazem for 6 months + statins + aspirin
Yoo	diltiazem indefinitely+ statins + beta blockers + aspirin

CCB: chronic calcium channel blockers therapy.

Table 2. **Pre- and intraoperative characteristics of the patients.**

	CCB (n = 502)	Non CCB (n = 230)	P value
Age (mean (sd))	62.28 (9.01)	70.18 (8.44)	<0.001
Male (n\%)	406 (80.9)	146 (63.5)	<0.001
Diabetes (n\%)	120 (23.9)	70 (30.4)	0.075
Prior MI (n\%)	156 (31.1)	83 (36.1)	0.209
Elective admission (n\%)	434 (86.5)	195 (84.8)	0.625
Renal insufficiency = (n\%)	30 (6.0)	21 (9.1)	0.162
LVEF < 0.35 = (n\%)	11 (2.2)	18 (7.8)	0.001
Target vessel = RCA (n\%)	116 (23.1)	102 (44.3)	<0.001
Number of grafts (mean (sd))	3.20 (0.73)	3.28 (1.48)	0.288
OPCABG = 1 (n\%)	38 (7.6)	0 (0.0)	<0.001
Proximal anastomosis on AA (n\%)	461 (91.8)	221 (96.1)	0.050
Trial (N/%)			
Petrovic	100 (19.9)	0 (0.0)	
RAPCO	257 (51.2)	51 (22.2)	
RSVP	82 (16.3)	0 (0.0)	
Stand-in-Y	28 (5.6)	179 (77.8)	
Yoo	35 (7.0)	0 (0.0)	

AA = ascending aorta; LVEF = left ventricular ejection fraction; MI = myocardial infarction; RCA = right coronary artery; OPCABG = off pump coronary bypass.

Table 3. **Cumulative incidence of outcomes of interest**

Group	Years of follow-up	MACE	Graft occlusion	Death	Myocardial infarction	Repeat revascularization
CCB(n = 502)						
	3	3.7[2-5.4]	0.9[0-2.2]	2.1[0.8-3.4]	0.2[0.0--0.6]	1.5[0.4--2.5]
	6	13.4[9.5-17.8]	9.6[4.2-14.9]	7.5[4.5-10.5]	2.0[0.7--3.3]	4.8[2.8--6.8]
	9	16.8[11.8-21.7]	14.3[4.0-24.7]	9.3[5.5-13.1]	2.4[0.9--3.8]	5.5[3.3--7.7]
No CCB (n = 230)						
	3	9.3[5.4-13.2]	8.6[4.2-12.9]	5.3[2.0-8.5]	3.1[0.8--5.3]	3.1[0.8-- 5.4]
	6	17.6[11-24.1]	21.4[13.0-29.8]	8.2[3.7-12.8]	4.2[1.1--7.2]	7.5[2.8--12.2]
	9	20.5[12-29]	38.9[16.5-61.2]	11.5[3.8-19.2]	4.2[1.1--7.2]	7.5[2.8--12.2]
Log-rank p		0.003	<0.001	0.09	0.02	0.129

** angiography available in n 243 patients in the CCB group and 200 in the non-CCB*

MACE: major adverse cardiac events.

Table 4. **Independent predictors of MACE.**

Variable	*Hazard Ratio*	*95 CI*	*p-value*
CCB	0.53	0.31-0.89	0.01
Age	1.01	0.99-1.04	0.31
Female gender	0.5	0.27-0.91	0.02
Diabetes	1.36	0.85-2.17	0.20
Prior MI	0.72	0.45-1.16	0.17
Elective admission	0.69	0.38-1.27	0.23
Renal insufficiency	1.11	0.55-2.25	0.77
LVEF < 0.35	2.97	1.27-6.93	0.01
N of grafts	0.85	0.61-1.17	0.31
OPCABG	1.52	0.26-9.08	0.64
Proximal anastomosis on AA	0.96	0.22-4.22	0.96

AA = ascending aorta; CCB = chronic calcium-channel blockers therapy; LVEF = left ventricular ejection fraction; MACE: major adverse cardiac events; MI = myocardial infarction; OPCABG = off pump coronary bypass.

Table 5. **Independent predictors of radial artery graft occlusion.**

Variable	*Hazard Ratio*	*CI.95*	*p-value*
CCB	0.20	0.08-0.50	< 0.001
Age	1.05	1.00-1.10	0.052
Female gender	0.32	0.14-0.74	0.007
Diabetes	0.51	0.20-1.30	0.15
Prior MI	0.97	0.45-2.08	0.92
Elective admission	0.54	0.23-1.28	0.15
Renal insufficiency	0.43	0.06-3.34	0.42
LVEF < 0.35	1.9	0.58-6.26	0.29
N of grafts	1.58	0.95-2.62	0.07
Proximal anastomosis on AA	0.99	0.13-7.74	0.99

AA = ascending aorta; CCB = chronic calcium-channel blockers therapy; LVEF = left ventricular ejection fraction; MACE: major adverse cardiac events; MI = myocardial infarction.

Figure 1. Cumulative incidence of major adverse cardiac events in the two groups.

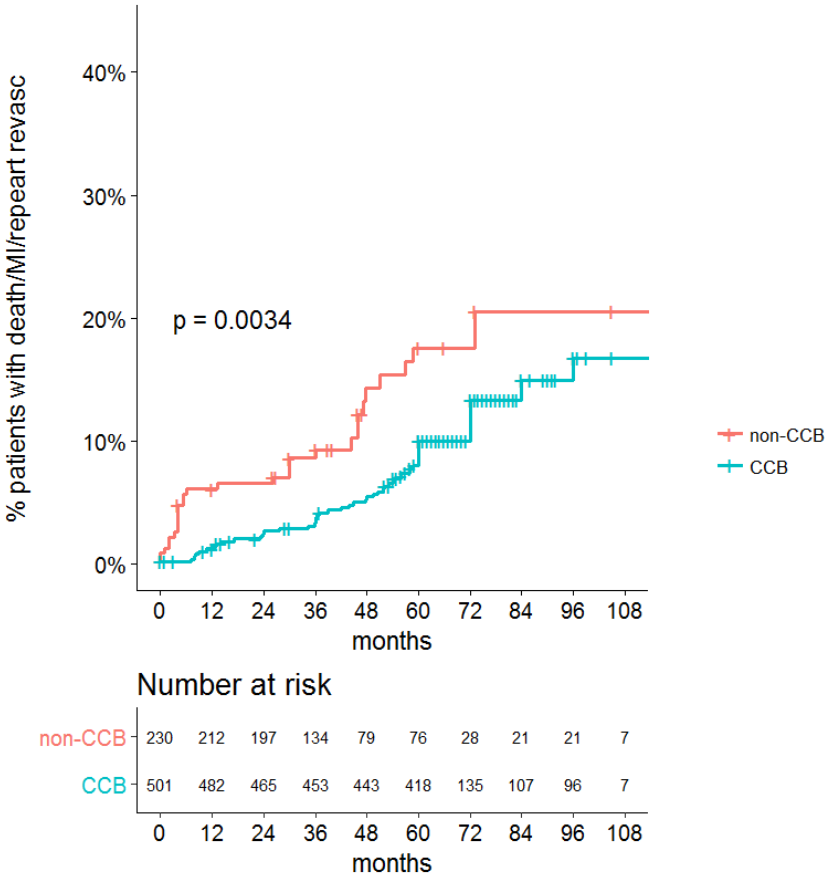

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Figure 2. Cumulative incidence of radial artery graft occlusion in the two groups.

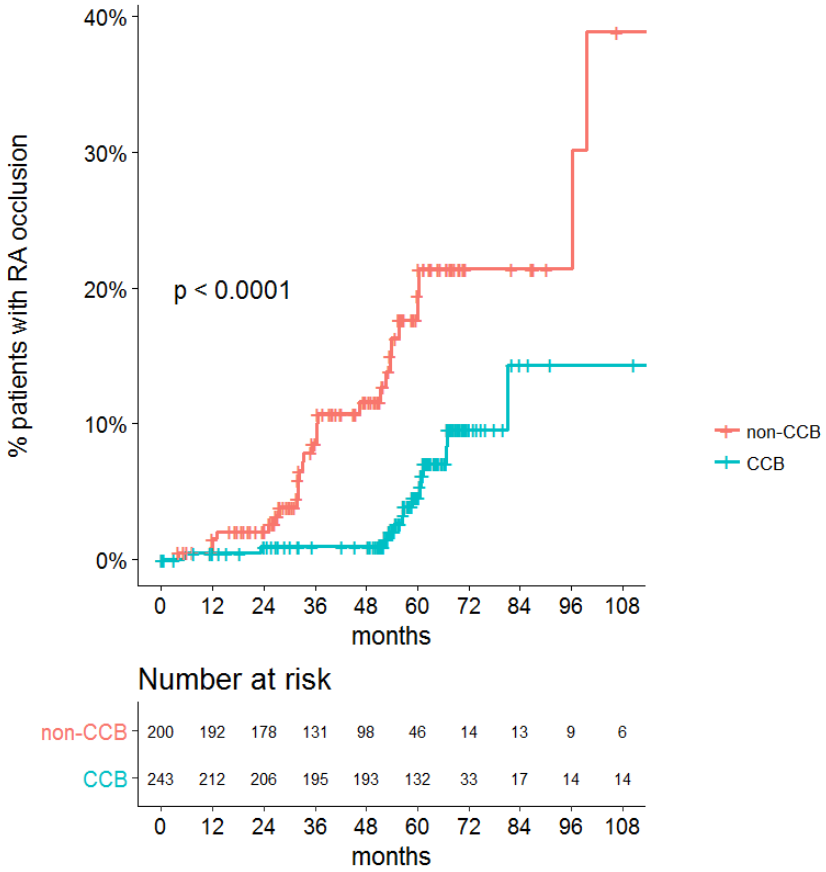

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Figure 3. Effect of the duration of chronic calcium blockers therapy on the risk of major adverse cardiac events. Reference point is 6-month duration which corresponds to the median duration in the overall sample. CCB therapy duration <6 months were associated with increased risk of MACE (Hazard Ratio, risk >1) while CCB therapy duration longer than 6 months were associated with lower risk (Hazard ratio, risk <1).

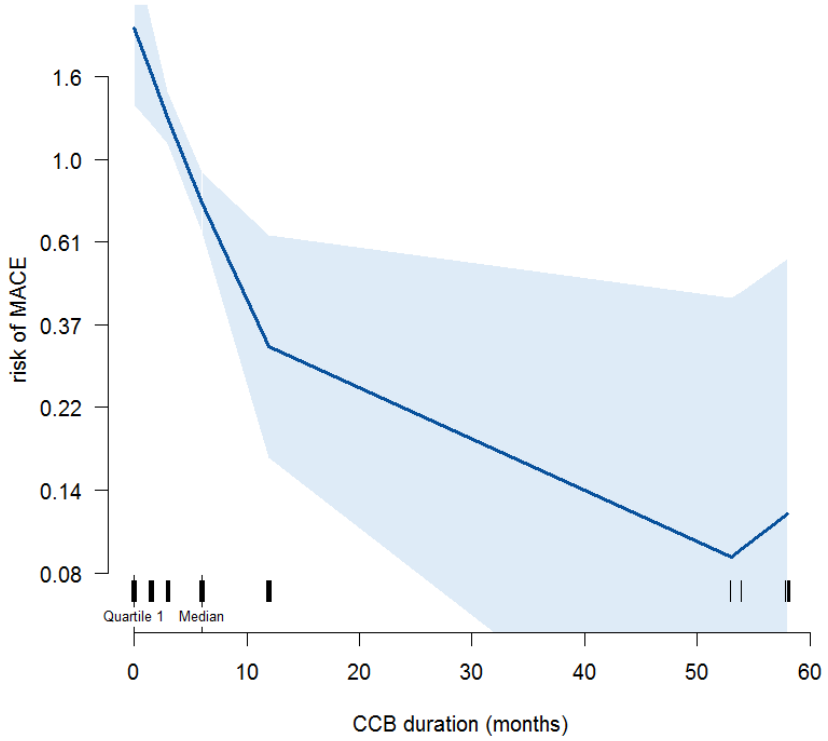

Figure 4. Effect of the duration of chronic calcium blockers therapy on the risk of radial artery graft occlusion. Effect of the duration of chronic calcium blockers therapy on the risk of major adverse cardiac events. Reference point is 6-month duration which corresponds to the median duration in the overall sample. CCB therapy duration <6 months were associated with increased risk of graft occlusion (Hazard Ratio, risk >1) while CCB therapy duration longer than 6 months were associated with lower risk of graft occlusion (Hazard ratio, risk <1).